REMARKS

Reconsideration and allowance of the subject application are respectfully requested.

By the above amendments, the specification is revised as requested by the Examiner. Specifically, the Examiner has requested that the specification be amended to include (1) the sequence identifiers for the sequence listing, (2) reference to the DNA construct pETB2360210, and (3) the priority data. We have amended the specification above to address this. Regarding the priority data, it is noted that reference to parent application 08/882,431 was submitted in the application transmittal letter (on page 1) accompanying the filing of this divisional application, and the information concerning the benefit claim was recognized by the Patent Office as shown by its inclusion on the filing receipt. Consequently, it is believed that a petition under 37 CFR 1.78(a) and the accompanying fee are not required.

Claim 100 is canceled without prejudice or disclaimer for the reasons stated below. Claim 101, the independent claim, is amended in two main ways: (1) to make clearer that the mutations of amino acids are chosen within a set of particular ranges of positions of amino acids – i.e., that only one mutation per range is contemplated, not the mutation of the entire 10-amino acid range; and (2) that the mutations may be done within at least two of the specified ranges of amino acid positions of SEB, located respectively at positions 40-50, 18-28, 55-65, 62-72, 84-94, 86-96, 89-99, 110-120 and 205-215. As noted below, this is supported by the specification at pages 19-21. (If the Examiner would like to suggest alternative language, she is invited to contact applicant's representative to talk about it.)

Claim 104 is amended to address the Examiner's objection under 35 U.S.C. §112, first paragraph. Specifically, claim 104 is amended to specify an isolated host cell.

Claims 102 and 107-114 are amended above to address the Examiner's objection under 35 U.S.C. §112, second paragraph, to clarify that amino acids are altered within the range of amino acids specified in each dependent claim. This concept is supported throughout the specification, for instance at pages 19-21.

New claim 115 is added which is dependent on claim 101 and specifies that amino acids are altered within the range of amino acids located at amino acid positions 40-50. This is fully supported throughout the specification, for instance at pages 19-21.

Regarding plasmids pETA489270C, pETB2360210, pETB899445P, and pETB899445C, these have all been deposited at the American Tissue Culture Collection (ATCC), Manassas, Virginia under the terms of the Budapest Treaty on June 4, 1997, and have been given the accession numbers noted above in the amendments to the specification. The undersigned confirms that these constructs were made under the Budapest Treaty and assurance is hereby given that all restrictions on the accessibility of these plasmids will be irrevocably removed by the applicant upon the granting of the patent. With entry of this amendment, claims 101-115 will be pending. No new matter is introduced by any of these amendments to the claims or specification, and entry and consideration are requested.

In the Office Action, claims 100 is rejected under 35 U.S.C. §101 as claiming the same invention as that of claim 10 in parent application U.S. Patent 6,713,284. We have canceled claim 100 above for this reason.

Claims 101-114 are rejected on the ground of obviousness-type double patenting over claims 1-30 of parent application U.S. Patent 6,713,284. The claims are not identical, but the Examiner is contending that they are not patentably distinct due to significant overlap in claim scope. We request that this rejection be held in abeyance until the claims have been found allowable. At that time if necessary we will file an appropriate terminal disclaimer.

Claims 101-114 are rejected under 35 U.S.C. §112, first paragraph, as containing new matter not included in the original written description, and claim 101 in particular. The Examiner is requesting us to point out where in the specification there is support for claim 101, since the "concept of combining mutations in this way . . . is not seen in the specification". Independent claim 101 is amended above, and now recites an isolated and purified superantigen toxin DNA fragment encoding Staphylococcal enterotoxin B (SEB) in which at least two of the following ranges of amino acid positions of SEB have each been altered at one amino acid: the range of amino acids located at positions 40-50, the

range of amino acids located at position 18-28, the range of amino acids located at position 55-65, the range of amino acids located at position 62-72, the range of amino acids located at position 84-94, the range of amino acids located at position 86-96, the range of amino acids located at position 89-99, the range of amino acids located at position 110-120 and the range of amino acids located at position 205-215, wherein the altered amino acids of SEB have been altered such that binding of said encoded SEB to the MHC class II receptor and T cell antigen receptor is altered.

Support for this language can be found on page 19, line 17 through page 21, line 17 of the specification, which states that

> The number of residues which can be altered can vary, preferably the number can be 1-2, more preferably 2-3, and most preferably 3-4 . . . The residues which can be altered can be within 5 amino acid residues of the central leucine of the hydrophobic loop (such as L45 of SEB), or within 5 residues of the amino acid residues of the polar binding pocket that can contact HLA-DR, (such as E67, Y89, or Y115 of SEB). . . . In addition, side chains of certain nonconserved receptor-binding surfaces, can also be altered when designing superantigen toxins with low binding affinities. These residues can include Y94 of SEB . . . .Furthermore . . . side chains of amino acids within 5 residues of the position represented by N23. . . ., N60 . . . , Y91. . . , and D210 of SEB. . . can be altered when designing superantigen toxins with low binding affinities.

Claim 101 as amended now recites a preferred embodiment of at least two of the mutations described in the specification at pages 19-21, within five amino acid residues, as directly supported by this section of the specification. The remaining claims 102-115 are dependent from claim 101. Claims 107-115 in particular recite each specific mutation respectively. This revision of claim 101 is believed to address the Examiner's concerns, and reconsideration of this rejection is requested.

Claims 100 and 104-106 are rejected under 35 U.S.C. §112, first paragraph, as non-enabled by the specification. Regarding claim 100, this claim has been canceled above, so this rejection is now moot. Regarding claims 104-106, we have amended claim 104 be amended to specify that the host cells are <u>isolated</u> host cells. This is believed to address the Examiner's concerns.

Claims 102 and 107-114 are rejected under 35 U.S.C., second paragraph, as being indefinite. We have amended these claims to better convey the amino acid positions to be mutated. Reconsideration is requested.

Lastly, claims 101, 103, 104 and 106 are rejected as anticipated by Bavari et al. ("Engineered Bacterial Superantigen Vaccines", Vaccines 96, Cold Spring Harbor Laboratory Press, pages 135-141, 1996). The Examiner's position is that Bavari et al. basically discloses the mutated SEB DNA of claim 101, where the mutations correspond to amino acid positions 40-50, 62-72, 84-94 and 110-120. The basis for this is that Bavari ostensibly discloses in Figures 3 and 4, and on page 138, the mutating of the SEB toxin in the hydrophobic loop, polar pocket, and disulfide loop to disrupt MHC class-II binding. The Examiner notes that Bavari does not explicitly disclose the claimed mutated SEB DNA fragments and corresponding vaccines, but that

> "production of these engineered vaccines would have required the claimed DNA fragments, expression vectors, host cells and methods of production. The reference clearly relies upon standard site-directed mutagenesis and recombinant production techniques that would have been well known to one of ordinary skill in the art at the time of the invention. The instant specification makes clear on pages 19-20 that the hydrophobic loop corresponds to positions 40-50 and the polar pocket corresponds to positions 62-72, 84-94, and 110-120." (See Office Action at page 8.)

That Bavari uses some standard techniques is not disputed. However, no specific methods were given in the paper as it was basically a brief review of its subject—that is all it was intended to be, and indeed all that it actually is. The lead named inventor, Dr. Robert Ulrich, who is also an author of the Bavari paper, has confirmed this. In fact, it turns out that the mutagenesis and recombinant protein production methods pertinent to the SEB DNA of the instant claims were not routinely selected out of a "cookbook"—i.e., standard methods and techniques—but had to be developed specifically for the end-product desired. For instance, see our specification in all of Examples 1-7 and the accompanying Figures, where many details of molecular modeling and animal modeling are provided—which models and testing provided the basis for determining the exact positions where mutations in the SEB DNA were required in order that binding of the

encoded SEB to the MHC class II receptor and T cell antigen receptor is necessarily altered. The choice of DNA to use, location of mutations, production, purification, characterization and testing of the recombinant proteins were unique to the SEB DNA and peptide product of our current claims. Bavari could not have been an anticipatory reference (nor an obviating one) because (1) none of these methods and the resultant data are provided and (2) the necessary sequences with mutations are not suggested in any way.

Bavari makes no disclosure or even reference to protein or DNA sequences or the particular range of amino acid mutations that are required in order that binding of the encoded SEB to the MHC class II receptor and T cell antigen receptor is necessarily altered. The Examiner has noted the sole reference in Bavari to a rSEB vaccine: "Rhesus monkeys were immunized with one dose ... of an rSEB vaccine in which three mutations were introduced into MHC class-II-binding sites." In the Bavari paper the terms "hydrophobic loop", "polar pocket" and "disulfide loop" were introduced, but again with no reference to any sequence or particular locations of mutations. The locations of the mutations are critical to our invention, as is made clear throughout our specification. Bavari's reference to three mutations in the MHC class-II-binding sites is far too vague to anticipate or render obvious our claims that require at least two mutations within the specific amino acid range positions of 40-50, 18-28, 55-65, 62-72, 84-94, 86-96, 89-99, 110-120 and 205-215.

The Examiner's comment that "[t]he instant specification makes clear on pages 19-20 that the hydrophobic loop corresponds to positions 40-50 and the polar pocket corresponds to positions 62-72, 84-94 and 110-120" can only be speculative in light of the sparseness of Bavari's description. Only with our specification's disclosure in hand would someone having ordinary skill in this art conclude that mutations within the range of amino acid positions 40-50, 62-72, 84-94 and 110-120 (or any of the others in claim 101) make sense. Bavari does not even discuss ranges of amino acid positions, or any specific amino acid positions, the alteration of which results in altered binding of the SEB to the receptors. A fair reading of Bavari—without the benefit of first knowing the contents of our patent specification—would not reveal our invention in any sort of

enabling way. Bavari fails to disclose the various features and limitations of claim 101, which include a **DNA fragment** encoding SEB in which **at least two** of the following **ranges of amino acid positions** of SEB have each been **altered at one amino acid**: the range of amino acids located at **positions 40-50**, the range of amino acids located at **positions 18-28**, the range of amino acids located at **positions 55-65**, the range of amino acids located at **positions 62-72**, the range of amino acids located at **positions 84-94**, the range of amino acids located at **positions 86-96**, the range of amino acids located at **positions 89-99**, the range of amino acids located at **positions 110-120** and the range of amino acids located at **positions 205-215**, wherein the altered amino acids of SEB have been altered **such that binding of said encoded SEB to the MHC class II receptor and T cell antigen receptor is altered**. (Emphasis added) Since every feature and limitation is not found in Bavari, we respectfully submit that our claims are patentable over this reference, and withdrawal of this rejection is believed to be in order.

In summary, all of the Examiner's outstanding rejections and objections have been addressed, and the application is believed to be in allowable form. Notice to that effect is earnestly solicited. No amendment made was related to the statutory requirements of patentability unless expressly stated herein, and no amendment made was for the purpose of narrowing the scope of any claim unless we argued above that such amendment was made to distinguish over a particular reference or combination of references.

If the Examiner has any questions or would like to make suggestions as to claim language, she is encouraged to contact Marlana K. Titus at (301) 977-

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